tract cancer, cystic fibrosis, hematologic malignancies, Duchenne muscular dystrophy, genitourinary cancers, gynecologic cancers, Emery-Dreifuss muscular dystrophy, Fanconi anemia, Hunter syndrome, neurofibromatosis type 1, neurofibromatosis type 2, familial melanoma, polycystic kidney disease, nevoid basal carcinoma, and von Hippel-Lindau disease.

40. The method of Claim 24 wherein the subject genes are mismatch repair genes.

41. The method of Claim 40 wherein the subject genes are selected from the group consisting of the MLH1, MSH2, MSH6, PMS1, and PMS2 genes; and said disease is or said disease susceptibility trait is for hereditary non-polyposis colon cancer.

42. The method of Claim 41 wherein the subject genes are the MLH1 gene and the MSH2 gene.

43. The method of Claim 24 wherein the amount of each wild-type protein expressed from each subject gene is determined by Western blot analysis, by immunoprecipitation and then by Western blot analysis, by flow cytometry, by EIA, by ELISA, by RIA, by competition immunoassay, by dual antibody sandwich assay, by chemiluminescent assay, by bioluminescent assay, by fluorescent assay, or by agglutination assay.

44. The method of Claim 24 which is automated.

54. A method according to Claim 25 wherein the ratio or ratios calculated in step (e) when compared to said mean or means of ratios indicates that the abnormally low level of said wild-type protein expressed by one of the subject genes in said sample is about 50% of the level of said wild-type protein in comparable samples from organisms unaffected by said disease or said disease susceptibility trait.

55. (Amended) A method according to Claim 25 wherein the ratio or ratios calculated in step **(e)** (e) when compared to said mean or means of ratios indicates that the **about 50% decrease in the** abnormally low **normal** level of said wild-type protein expressed by one of the subject genes in said sample is about 50% ± 20% of the level of said wild-type protein in comparable samples from organisms unaffected by said disease or said disease susceptibility trait.

56. (Amended) A method according to Claim 25 wherein the ratio or ratios calculated in step **(e)** (e) when compared to said mean or means of ratios indicates that the **about 50% decrease in the** abnormally low **normal** low level of said wild-type protein expressed by one of the subject genes in said sample is about 50% ± 15% of the level of said wild-type protein in comparable samples from organisms unaffected by said disease or said disease susceptibility trait.

57.   (Amended) A method according to Claim 25 wherein the ratio or ratios calculated in step **(e)** ~~(e)~~ when compared to said mean or means of ratios indicates that the **about 50% decrease in the** ~~abnormally low~~ **normal** level of said wild-type protein expressed by one of the subject genes in said sample is about 50% ± 10% of the level of said wild-type protein in comparable samples from organisms unaffected by said disease or said disease susceptibility trait.

~~58.   The method of Claim 35 wherein said cells are peripheral blood lymphocytes.~~

59.   The method of Claim 40 wherein the normal biological sample comprises peripheral blood lymphocytes.

60.   The method of Claim 42 wherein the normal biological sample comprises peripheral blood lymphocytes.

61.   The method of Claim 24 wherein said mutation is selected from the group consisting of truncation-causing mutations and mutations that cause allelic loss.

PROPOSED AMENDMENTS

DO NOT ENTER

24.   (Four times amended) A method of detecting a
disease or a disease susceptibility trait in an organism,
wherein said disease or said disease susceptibility trait is
known to be associated with a germline mutation **that causes an
about 50% decrease in the level of wild-type protein normally
expressed by** ~~in~~ one of two or more subject genes~~, and wherein
said germline mutation is selected from the group consisting of
mutations that cause an about 50% decrease in the level of wild-
type protein normally expressed by a subject gene~~, **comprising**:

   (a) isolating a biological sample **containing normal
cells** from said organism;

   (b) preparing a lysate of said normal cells;

   **(c) preparing a protein extract from said lysate of
said normal cells;**

   (d) ~~(b)~~ immunologically quantitating the amount of
wild-type protein in said **protein extract of said normal cells**
~~sample~~, that is expressed by each of the subject genes;

   (e) ~~(c)~~ calculating the ratio of the amount of the
wild-type protein expressed by one of said subject genes in said
normal cells ~~sample~~, to the amount of wild-type protein
expressed by the other subject gene in said **normal cells** ~~sample~~,
or to each of the amounts of wild-type protein expressed by each
of the other subject genes in said **normal cells** ~~sample~~;

(f) (d) determining whether the ratio or ratios calculated in step (e) (e) reflects or reflect an **about 50% decrease in the** ~~abnormally low~~ **normal** level of a wild-type protein expressed by either of the subject genes, or by any of the subject genes in said **normal cells** ~~sample~~; and

(g) (e) concluding that if the ratio or ratios calculated in step (e) (e) indicates or indicate that there is an **about 50% decrease in the** ~~abnormally low~~ **normal** level of a wild-type protein expressed by one of the subject genes in said **normal cells** ~~sample~~, that that subject gene contains a germline mutation in one of its alleles, and that the subject organism is affected by the disease or the disease susceptibility trait associated with said germline mutation.

25.   (Twice amended) The method of Claim 24 wherein step **(f)** ~~(d)~~ comprises comparing the ratio or ratios calculated in step **(e)** ~~(e)~~ to a comparable mean or means of ratios calculated from the amounts of wild-type proteins expressed by the subject genes in comparable biological samples from organisms of the same taxonomic classification as the subject organism, wherein said organisms of the same taxonomic classification as the subject organism are unaffected by said disease or by said disease susceptibility trait.

26.   The method of Claim 24 wherein said organism is a vertebrate.

27. The method of Claim 26 wherein said vertebrate is a mammal.

28. The method of Claim 27 wherein said mammal is a human.

32. (Twice amended) The method of Claim 24 wherein said mutation is selected from the group consisting of nonsense mutations, frameshift mutations, promoter mutations, enhancer mutations, splice site mutations, null mutations, and poly-A tail mutations.

33. (Twice amended) The method of Claim 24 wherein said biological sample is selected from the group consisting of body fluids, **and** tissue specimens, tissue extracts, normal cells, lysates of normal cells, normal cell extracts, and supernatants from lysates of normal cells.

34. The method of Claim 33 wherein said body fluids are selected from the group consisting of blood, serum, plasma, semen, breast exudate, gastric secretions, fecal suspensions, bile, saliva, tears, sputum, mucous, urine, lymph, cytosols, ascites, pleural effusions, amniotic fluid, bladder washes, bronchoalveolar lavages, and cerebrospinal fluid.

35. (Twice amended) The method of Claim **24** ~~33~~ wherein **said normal** ~~the~~ cells are peripheral blood lymphocytes~~; the cell lysates are lysates of peripheral blood lymphocytes; the cell extracts are from peripheral blood lymphocytes; and the supernatants are from lysates of peripheral blood lymphocytes~~.

~~36. (Amended) The method of Claim 24 wherein said biological sample is selected from the group consisting of normal cells, lysates of normal cells, and supernatants from lysates of normal cells.~~

37. The method of Claim 24 wherein said method is diagnostic or diagnostic/prognostic for cancer or for susceptibility to cancer.

38. The method of Claim 24 wherein the subject genes are selected from the group consisting of ATM, APC, BRCA1, BRCA2, CFTR, c-myb, dystrophin, E-cadherin, EMD, FAA, IDS, MLH1, MSH2, MSH6, NF1, NF2, p16, PKD1, PKD2, PMS1, PMS2, PTCH, TGFBR2, and VHL genes.

39. The method of Claim 24 wherein said disease is, or said susceptibility trait is for a disease selected from the group consisting of ataxia-telangiectasia, hemangioblastoma, renal cell carcinoma, pheochromocytoma, colon cancer, colorectal cancer, gastrointestinal cancer, breast cancer, ovarian cancer, endometrial cancer, prostate cancer, pancreatic cancer, biliary